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Hemoglobin S/O_{ARAB}: Thirteen New Cases and Review of the Literature

Sherri A. Zimmerman,[1]* Erin E. O'Branski,[1] Wendell F. Rosse,[2] and Russell E. Ware[1]

[1]Division of Pediatric Hematology/Oncology, Department of Pediatrics, Duke University Medical Center, Durham, North Carolina
[2]Division of Hematology, Department of Medicine, Duke University Medical Center, Durham, North Carolina

Hemoglobin S/O_{Arab} (Hb S/O_{Arab}) is a rare compound heterozygous hemoglobinopathy characterized by the presence of two variant β-globin chains: β^{6}Glu → Val (Hb S) and β^{121}Glu → Lys (Hb O_{Arab}). The diagnosis of Hb S/O_{Arab} requires electrophoresis on both cellulose acetate and citrate agar, since Hb O_{Arab} co-migrates with Hb C at alkaline pH and close to Hb S at acidic pH. To date only case reports and small series of patients with Hb S/O_{Arab} have been described. To better characterize the clinical and laboratory aspects of this unusual disorder, we reviewed the Duke University Medical Center experience. We identified 13 African-American children and adults with Hb S/O_{Arab} ranging in age from 2.7 to 62.5 years. All patients had hemolytic anemia with a median Hb of 8.7 gm/dL (range 6.1–9.9 gm/dL), and a median reticulocyte count of 5.8% (range 1.2–10.3%). The peripheral blood smear typically showed sickled erythrocytes, target cells, polychromasia, and nucleated red blood cells. All 13 patients have had significant clinical sickling events including acute chest syndrome (11), recurrent vasoocclusive painful events (10), dactylitis (7), gallstones (5), nephropathy (4), aplastic crises (2), avascular necrosis (2), leg ulcers (2), cerebrovascular accident (CVA) (1), osteomyelitis (1), and retinopathy (1). Four patients have died, including two from pneumococcal sepsis/meningitis at ages 5 and 10 years, one of acute chest syndrome at age 14 years, and one of multiorgan failure at age 35 years. We conclude that Hb S/O_{Arab} disease is a severe sickling hemoglobinopathy with laboratory and clinical manifestations similar to those of homozygous sickle cell anemia. Am. J. Hematol. 60:279–284, 1999. © 1999 Wiley-Liss, Inc.

Key words: hemoglobin S; hemoglobin O_{Arab}; sickle cell disease

INTRODUCTION

Hemoglobin O_{Arab} (Hb O_{Arab}) is an abnormal hemoglobin characterized by the substitution of lysine for glutamic acid at position 121 of the β-globin chain [1]. The electrophoretic mobility of Hb O_{Arab} is similar to Hb C, Hb E, and Hb A_2 on cellulose acetate at alkaline pH. In contrast, Hb O_{Arab} migrates close to Hb S on citrate agar at acidic pH [2].

Heterozygotes for Hb O_{Arab} trait have been reported in Saudi Arabia [3], North Africa [4], Sudan [5–7], Yugoslavia [8], Bulgaria [9], Jamaica [10], the Mediterranean [11], and the United States [12]. These persons are clinically asymptomatic and typically have no laboratory abnormalities. Patients homozygous for Hb O_{Arab} are clinically asymptomatic but have a mild compensated hemolytic anemia [4–6,8,13–15]. Typical laboratory findings include a Hb of 10–12 gm/dL, reticulocyte counts of 2–5%, and serum bilirubin concentrations of 1.8–3.5 mg/dL [5,6,8,14].

The inheritance of Hb O_{Arab} in combination with sickle Hb, a compound heterozygous condition known as Hb S/O_{Arab}, was first described in 1960 in an Arabic boy with severe hemolytic anemia and recurrent painful episodes [16]. Since then, case reports and small series of patients with Hb S/O_{Arab} disease have been described [5,6,10,13,15,17,18]. These patients with HbS/O_{Arab}, mostly of Middle Eastern descent, have had clinical and laboratory manifestations characteristic of a sickling dis-

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*Correspondence to: Sherri A. Zimmerman, M.D., Box 2916, Duke University Medical Center, Durham, NC 27710. E-mail: Zimme008@mc.duke.edu

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order with hemolytic anemia, jaundice, painful episodes, and less commonly, pneumonia and sepsis [4,5,11,13,15]. A total of nine African-American patients with Hb S/O_{Arab} have been reported previously, but several were incompletely characterized. The clinical and laboratory characteristics of these African-American patients were similar to the patients of Arabic descent [2,10,12,17, 19–22].

To date, no large series of patients with Hb S/O_{Arab} has been reported. To better characterize the clinical and laboratory aspects of this unusual disorder, we reviewed the Duke University Medical Center experience. We identified 13 African-American children and adults with Hb S/O_{Arab} disease and now report their laboratory findings and clinical manifestations. Based on this review, we conclude that Hb S/O_{Arab} is a severe sickling disorder similar to homozygous sickle cell anemia.

METHODS

Patient Identification

The computer database for over 1,000 adult and pediatric patients followed by the Duke University Comprehensive Sickle Cell Center was used to identify patients. The laboratory diagnosis of Hb S/O_{Arab} was established by the Hemolytic Anemia Diagnostic Laboratory at Duke University Medical Center. Hb electrophoresis was performed on cellulose acetate at pH 8.6 and citrate agar at pH 6.2. When possible, family studies were used to verify the diagnosis.

Data Collection

Office and hospital charts were reviewed for demographic data including age, gender, and race. Clinical complications were recorded including painful vasoocclusive events, gallstones, splenic sequestration, acute chest syndrome (ACS), sepsis, avascular necrosis, priapism, CVA, leg ulcers, retinopathy, nephropathy, and aplastic crisis. The use of erythrocyte transfusions, in particular chronic transfusions, was also noted.

Laboratory Evaluation

Baseline laboratory parameters were recorded for each patient, including Hb, mean corpuscular volume (MCV), reticulocyte count, fetal hemoglobin (Hb F), total bilirubin concentration, and peripheral blood smear findings. Up to five of the most recent laboratory studies were used to determine a representative blood count for each patient. For the three youngest patients, only studies obtained after 2 years of age were included. For patients receiving chronic transfusions or hydroxyurea, baseline laboratory values obtained prior to treatment were used.

Statistics

Descriptive statistics to determine mean and median laboratory values were performed using the Primer of Biostatistics (McGraw-Hill, New York).

RESULTS

Patient Population

We identified 13 patients with Hb S/O_{Arab} from nine different families, ranging in age from 2.7 to 62.5 years. All patients were African-American and 9 of the 13 were female. Historically, at least six of the patients had been diagnosed incorrectly as having Hb SC disease before evaluation at our center, and two others were misdiagnosed as having Hb S with Hb C_{Harlem}. An example of the Hb electophoresis pattern for Hb S/O_{Arab} on both cellulose acetate and citrate agar is shown in Figure 1.

Laboratory Results

Table I summarizes the laboratory data for the 13 patients. The Hb concentration ranged from 6.1 to 9.9 gm/dL, median 8.7 gm/dL. The MCV ranged from 64 to 91 fL, median 85 fL. Patients #2 and #5 have a lower MCV due to known concomitant α-thalassemia, two gene deletion. All patients had evidence of hemolytic anemia with reticulocytosis and mild hyperbilirubinemia. The median reticulocyte count was 5.8% (range 1.2–10.3%) and the median total bilirubin concentration was 2.0 mg/dL (range 1.2–7.2 mg/dL). Most patients had increased Hb F with a median of 6.7% (range 0.6–20.3%). A representative peripheral blood smear is shown in Figure 2 and demonstrates sickled erythrocytes, target cells, polychromasia, and a Howell-Jolly body. Five of the 13 patients, including the two youngest patients, had Howell-Jolly bodies identified in erythrocytes, documenting functional asplenia.

Clinical Events

All of the patients with Hb S/O_{Arab} had clinical sickling events with significant morbidity (Table I). Eleven of the 13 patients (85%) had at least one episode of acute chest syndrome, and many had recurrent episodes. One patient (#7) died from ACS at age 14 years and two others developed pulmonary fibrosis by early adulthood. Most patients had dactylitis or recurrent painful vasoocclusive crises requiring medical treatment. Febrile illnesses were quite common, and two patients (#4 and #6) died from pneumococcal sepsis and meningitis at age 5 and age 10 years, respectively. Although neither patient was receiving penicillin prophylaxis at the time of pneumococcal infection, patient #4 received penicillin until her fifth birthday, just two weeks before her death. Patient #11 died of multiorgan failure at age 35 years. Five of the 13 patients had gallstones requiring cholecystec-

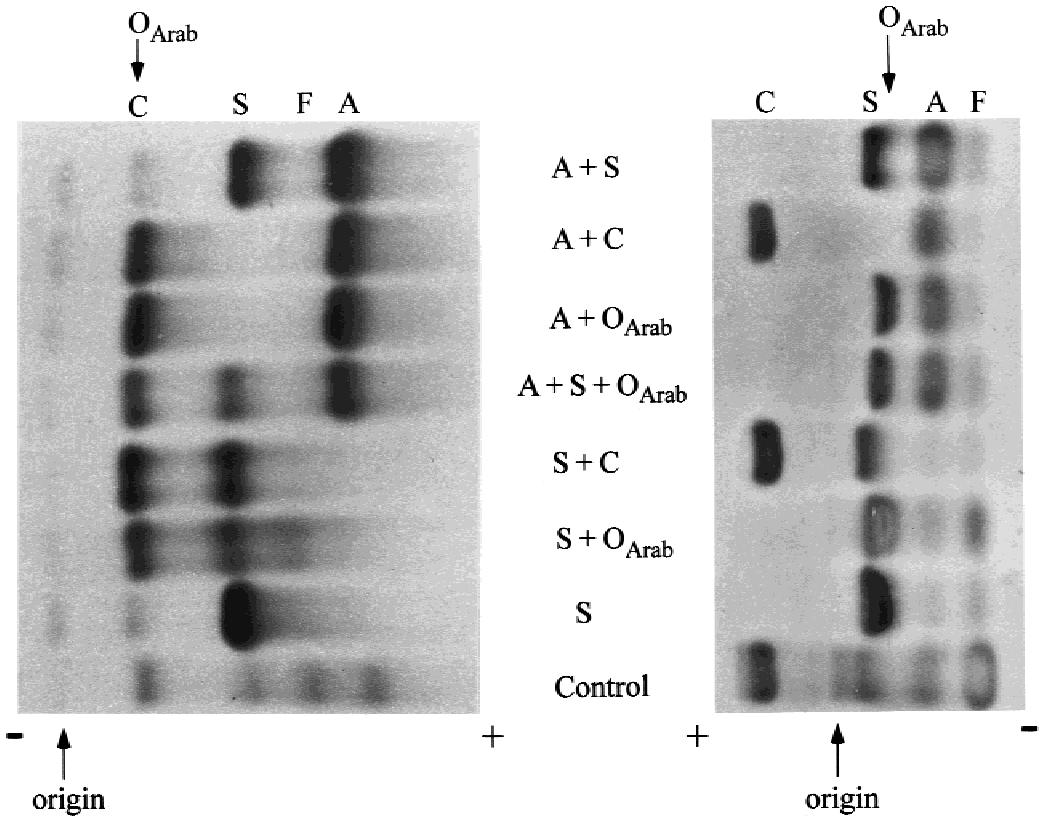

Fig. 1. Hb electrophoresis pattern of Hb O_{Arab}. On cellulose acetate (pH 8.6) as shown on the left, Hb O_{Arab} migrates in the same position as Hb C, Hb C_{Harlem}, Hb E, and Hb A_2. On citrate agar (pH 6.2) shown on the right, however, Hb O_{Arab} migrates very close to Hb S. The characteristic crescent-shaped band of Hb O_{Arab} can be seen most easily on citrate agar in the patient with Hb O_{Arab} trait.

tomy, and 4 patients developed sickle nephropathy, including two with chronic renal failure. One young boy (#1) had a cerebrovascular accident at age 2 years and now receives chronic transfusions. Other complications found in smaller numbers of patients include aplastic crisis (2), avascular necrosis of the hips (2), leg ulcers (2), osteomyelitis (1), and retinopathy (1).

DISCUSSION

Since the initial description of Hb S/O_{Arab} in 1960, only case reports and small series of patients have been described. To our knowledge, only 26 patients with Hb S/O_{Arab} have been reported previously, but often complete laboratory and clinical details were not provided. The majority of the patients have been of Arabic descent, including the largest series of 11 patients. A total of nine African-American patients have been described [2,10,12,17,19–22], with no clear differences compared with Arabic patients. Patients with Hb S/O_{Arab} typically have had moderate to severe hemolytic anemia with variable clinical manifestations. Splenomegaly was sometimes noted [12,13,16,17], but splenic sequestration has only been reported in a single patient with Hb S/O_{Arab} disease [18].

Our cohort of 13 African-American patients with Hb S/O_{Arab} represents the largest single series reported to date. All of our patients had a partially compensated hemolytic anemia with a median Hb concentration of 8.7 gm/dL and reticulocyte count of 5.8%. This is a higher average Hb concentration and lower reticulocyte count than that observed in most patients with homozygous sickle cell anemia, suggesting that Hb S/O_{Arab} is associated with less hemolysis than Hb SS [23]. The peripheral blood smear of all of our patients showed numerous sickled erythrocytes, target cells, polychromasia, and nucleated red blood cells, however, similar to Hb SS (Fig. 2). In addition, Howell-Jolly bodies were identified in several of our patients, an observation not noted in previous cases. Each of our patients had clinical sickling events with significant morbidity, including episodes of ACS, painful vasoocclusive crisis, sepsis, gallstones, and sickle nephropathy, despite the fact that the median age of our patients is only 15 years. Three deaths occurred in childhood, two of pneumococcal sepsis and meningitis at age 5 and age 10 years, and the other of acute chest syndrome

TABLE I. Clinical and Laboratory Characteristics of 13 Patients With Hb S/O_{Arab}*

Patient #	Age (years)	Sex	Hb (gm/dL)	MCV (fL)	Retic (%)	Bilirubin (mg/dL)	Hb F (%)	Erythrocyte morphology	Clinical events
1	2.7	M	9.5	83	7.2	1.6	14.0	ISC, target, HJ bodies, NRBC	ACS, CVA
2	3.2	F	9.9	64	6.2	3.1	20.3	ISC, target, HJ bodies, microcytosis, NRBC	Dactylitis, developmental delay
3	3.7	M	9.5	85	4.5	6.3	17.8	ISC, target, poikilocytosis	Aplastic crisis, pulmonary stenosis
4	5.0	F	8.4	90	NA	7.2	9.0	ISC, target, poikilocytosis, anisocytosis, NRBC, HJ bodies	ACS, sepsis/meningitis (death), dactylitis, VOC
5	9.5	M	8.9	67	3.2	1.4	5.8	ISC, target, HJ bodies, microcytosis, NRBC	ACS, dactylitis, VOC
6	10.0	F	8.7	NA	10.3	1.6	1.1	ISC, target, hypochromia, microcytosis, NRBC	ACS, sepsis/meningitis (death), dactylitis, VOC
7	15.0	F	9.7	83	2.4	NA	NA	ISC, target, NRBC	ACS (death), dactylitis, VOC
8	19.0	M	6.1	86	5.8	1.2	NA	ISC, target, poikilocytosis, microcytosis, NRBC	ACS, CRF, dactylitis, GS, osteomyelitis, VOC
9	25.0	F	9.2	88	6.0	3.0	0.6	schistocytes, helmets	ACS, aplastic crisis, AVN, GS, nephropathy, retinopathy, dactylitis, VOC
10	27.9	F	8.4	91	1.2	1.7	8.5	ISC, target, microcytosis, NRBC	ACS, AVN, VOC
11	35.7	F	7.0	86	8.4	2.1	3.7	ISC, target, HJ bodies, microcytosis, anisocytosis, NRBC	ACS, CHF, DVT, GS, leg ulcers, pulmonary fibrosis, VOC, multiorgan failure (death)
12	37.4	F	8.0	85	5.8	1.9	1.7	ISC, target, hypochromia, NRBC	ACS, GS, nephropathy, pulmonary fibrosis, VOC
13	62.5	F	7.2	94	5.2	2.1	6.7	NA	ACS, CRF, GS, leg ulcers, VOC

*Hb, hemoglobin; MCV, mean corpuscular volume; Retic, reticulocyte count; Hb F, fetal hemoglobin; ISC, irreversibly sickled cells; HJ, Howell Jolly bodies; NRBC, nucleated red blood cells; NA, not available; ACS, acute chest syndrome; CVA, cerebrovascular accident; VOC, vasoocclusive crisis; CRF, chronic renal failure; GS, gallstones; AVN, avascular necrosis; CHF, congestive heart failure; DVT, deep vein thrombosis.

at age 14 years. An additional patient died of multiorgan failure at age 35 years.

The clinical severity observed in patients with Hb S/O_{Arab} may be related to the observation that erythrocytes containing Hb S and Hb O_{Arab} have a lower gelling point and lower oxygen affinity than cells containing Hb S with Hb A or Hb C [10,12]. Hb O_{Arab}, unlike Hb A or Hb C, stabilizes intracellular polymerization of Hb S and leads to formation of irreversibly sickled cells [10,20]. The mutation in Hb O_{Arab} is at position 121 of the β-globin chain, which is a contact point for polymer formation [24]. This is the same nucleotide altered in Hb D-Los Angeles (D-Punjab, β^{121}Glu → Gln), which also facilitates polymerization of Hb S and leads to a severe clinical sickling disorder [25]. We hypothesize that the strong sickling tendency of erythrocytes containing Hb S and Hb O_{Arab}, coupled with the higher average Hb concentration, makes Hb S/O_{Arab} a severe clinical sickling disorder.

Accurate diagnosis of Hb S/O_{Arab} requires electrophoresis at both alkaline and acidic pH, since Hb O_{Arab} comigrates with Hb C on cellulose acetate at alkaline pH and migrates very close to Hb S on citrate agar at acidic pH (Fig. 1). Several of our patients had been originally diagnosed incorrectly as having Hb SC disease. The clinical findings in patients with Hb S/O_{Arab} disease are much more severe than those typical for Hb SC disease, however, so the diagnosis of Hb SC made by cellulose acetate must always be confirmed by electrophoresis on citrate agar. Family studies may also be informative because it is often easier to separate Hb O_{Arab} from Hb A than from Hb S (Fig. 1). Differentiating Hb O_{Arab} from Hb C_{Harlem}, a Hb variant with two substitutions in the β chain, can be difficult because both abnormal hemoglobins comigrate with Hb C on cellulose acetate and with Hb S on citrate agar [26]. By family studies, however, the two variants can be distinguished because heterozygotes for Hb O_{Arab} have a negative sickle preparation, whereas persons with Hb C_{Harlem} trait are positive since Hb C_{Harlem} has both the sickle mutation (β^{6}Glu → Val) and the Korle Bu mutation (β^{73}Asp → Asn) [26].

The advent of newborn screening for hemoglobinopathies should identify infants with Hb O_{Arab} at birth. During the time period of 1986–1993, 10 cases of Hb A/O_{Arab} were identified in North Carolina, whereas only one case of Hb S/O_{Arab} was found (Personal communication, Robbie Safko, December 1997). During this same time period, 15,286 cases of Hb AS were identified. In our state, therefore, the gene frequency of Hb O_{Arab} is approximately 1,300 times less common than Hb S.

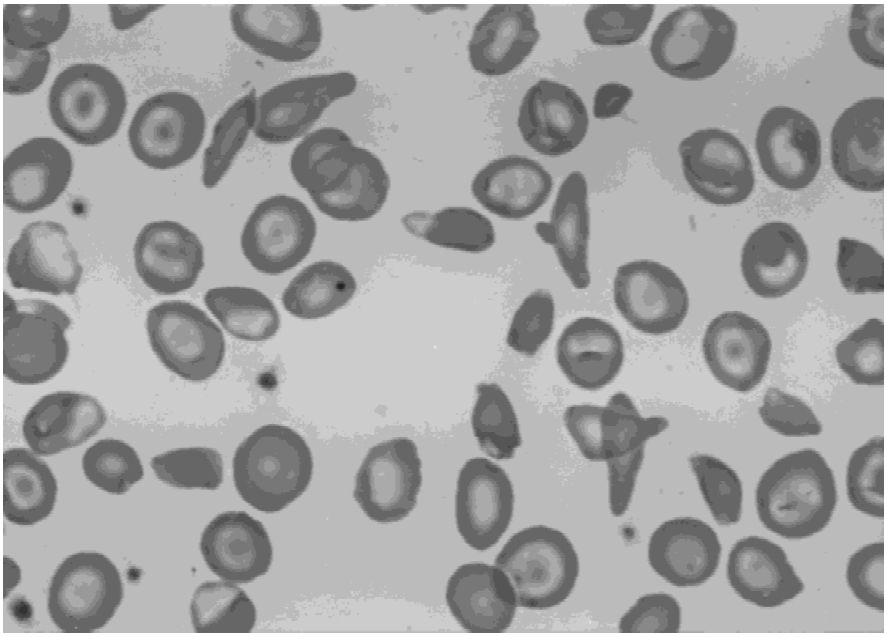

Fig. 2. Peripheral blood smear findings in a patient with Hb S/O_{Arab} disease. Target cells, irreversibly sickled cells, and polychromasia are present. A Howell-Jolly body, a marker of functional asplenia, is also seen.

Based on annual birth rates [27], we estimate that 1,500–2,000 infants with sickle cell disease are born yearly in the United States; therefore it is possible that several infants with Hb S/O_{Arab} are born each year. Clinicians must recognize that Hb S/O_{Arab} is a severe sickling hemoglobinopathy and counsel families appropriately. Penicillin prophylaxis and pneumococcal immunizations should be prescribed, along with careful clinical follow-up.

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